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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/786,988	01/23/1997	DANIEL P. LITTLE	24736-2001D	5922

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EXAMINER	
GAKH, YELENA G	
ART UNIT	**PAPER NUMBER**
1743	

DATE MAILED: 01/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/786,988	LITTLE ET AL.	
	Examiner	Art Unit	
	Yelena G. Gakh, Ph.D.	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *108-146* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *108-146* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/08/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. RCE and Amendment filed on 12/08/04 are acknowledged. Claims 108-146 are pending in the application.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 140-143 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method comprising "depositing a defined and controlled volume of another solution comprising an analyte" on more than one spot, does not reasonably provide enablement for the method where there is just one spot at which the analyte is deposited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. There is no way for a routineer in the art to obtain reproducible MALDI spectra, if only one spot contains the analyte.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 141-143 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims appear to recite a characteristic of the spot array, rather than an active method step. The claims should recite performing MALDI analysis for all spots of the array, which may be followed by such limitation, as recited now in the claims, e.g. "the automated process of claim 135, which further comprises obtaining MALDI mass spectra directly from the spots in the array, wherein the MALDI mass spectra are reproducible".

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. **Claims 108-118, 120-123, 125, 132-141 and 143-146** are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicola et al. (Rapid Commun. Mass Spectrom., 1995) in view of Hayes et al. (US 5,658,802, IDS).

Nicola teaches "application of the fast-evaporation sample preparation method for improving quantification of angiotensin II by matrix-assisted laser desorption/ionization". Nicola emphasis increased reproducibility of mass spectra from spot to spot obtained by depositing an array of 2.5-10 μL droplets of the matrix on the MALDI substrate, drying the spots and applying ~ 1.0 μL of analyte/matrix solution on top of the dried matrix spots.

Nicola does not teach depositing drops of 0.2-20 nL or perrfotmin MALDI MS for nucleic acids.

Hayes teaches "method and apparatus for making miniaturized diagnostic arrays" using electro-mechanical or piezoelectrical dispensers to place extremely small drops (10 pl to 1 nl) of fluid on substrates to form diagnostic arrays. Hayes indicates, "the invention thus provides a highly accurate, rapid and repeatable method of placing extremely small drops (10 pl to 1 nl) of fluid reagent on substrates to form diagnostic arrays. By using such small drops and accurately positioning them on the substrate, test strips can be formed which have a larger number of probes located within a smaller area than is achievable with prior methods" (col. 2, lines 49-55). Different electro-mechanical dispensers comprising vesicles with chambers and transducers are disclosed in col. 2.

It would have been obvious for any person of ordinary skill in the art to modify Nicola's MALDI MS analysis by using Hayes' method of depositing very small droplets (less than 1 nL) of the matrix material because, because this further increases reproducibility of the spots, as indicated by Hayes, and to apply this improved method for nucleic acids analysis, because MALDI MS is a well recognized method of analysis for DNA.

10. **Claims 108-118, 120-123, 125, 132-141 and 143-146** are rejected under 35 U.S.C. 103(a) as being unpatentable over Vestal (US 5,498,545, IDS) in view of Vorm et al. (Anal. Chem., 1994) and Hayes.

Vestal teaches an automated MALDI MS analysis for a plurality of samples, specifically DNA analytes, deposited as 100 nL droplets (col. 4, line 59) on a MALDI plate made of "stainless steel or other suitable electrically conducting material" (col. 3, lines 57-58). The samples are prepared as mixtures of the analytes with MALDI matrix.

Vestal fails to teach depositing MALDI matrix without the analyte and allowing the spot to dry before depositing the analyte.

Vorm teaches a "fast evaporation" method of MALDI matrix deposition on a MALDI plate, comprising depositing ~ 0.5 μL drop of the matrix (ferulic acid, sinapic acid, etc.) on the MALDI stainless steel probe tip and allowing the spot to dry before applying a droplet of an analyte, indicating "improved resolution and very high sensitivity in MALDI TOF of matrix

surfaces made by fast evaporation" (Title). The solvents are acetone, acenotrile, methoanol, acetic acid and trifluoroacetic acid (page 3282).

It would have been obvious for any person of ordinary skill in the art to modify Vestal's method of MALDI MS analysis by Vorm's method of depositing MALDI matrix as a droplet and allowing it to dry before depositing the analyte, because Vorm specifically indicates that it improves resolution and provides very high sensitivity in MALDI TOF analysis.

Vestal in view of Vorm do not teach depositing drops of 0.2-20 nL.

Hayes teaches "method and apparatus for making miniaturized diagnostic arrays" using electro-mechanical or piezoelectrical dispensers to place extremely small drops (10 pl to 1 nl) of fluid on substrates to form diagnostic arrays. Hayes indicates, "the invention thus provides a highly accurate, rapid and repeatable method of placing extremely small drops (10 pl to 1 nl) of fluid reagent on substrates to form diagnostic arrays. By using such small drops and accurately positioning them on the substrate, test strips can be formed which have a larger number of probes located within a smaller area than is achievable with prior methods" (col. 2, lines 49-55). Different electro-mechanical dispensers comprising vesicles with chambers and transducers are disclosed in col. 2.

It would have been obvious for any person of ordinary skill in the art to modify Vestal-Vorm's MALDI MS analysis, including analysis of DNA by using Hayes' method of depositing very small droplets (less than 1 nL) of the matrix material because, as Hayes indicated, it allows creating a plurality of highly reproducible and volume-controlled spots, which is essential for obtaining reproducible MALDI spectra, the importance of which is well recognized in the art.

12. **Claims 119, 124, 126-131,** are rejected under 35 U.S.C. 103 (a) as being unpatentable over Nicola in view of Hayes or over Vestal in view of Vorm and Hayes, as applied to claims 108-118, 120-123, 125, 132-141 and 143-146 above, and further in view of Hancock et al. (US 5,716,825, IDS).

Nicola in view of Hayes or Vestal in view of Vorm and Hayes do not specifically disclose other matrices, or materials of the substrate other than steel.

Hancock discloses an integrated nucleic acid analysis system for MALDI-TOF MS, and describes in particular a thin film sample support, which is a substantially "planar manifold made of a non-conducting material that includes a microchannel and other necessary components of a

miniturized sample preparation compartment, an interface to non-consumable parts, and an ionization surface for MALDI-TOF MS. Such a miniaturized device may be formed from a variety of materials (e. g., **silicon, glass, low cost polymers**) by techniques that are well known in the art (e.g., micromachining, chemical etching, laser ablation, and the like)" (col. 4,11. 34-44). Hancock further describes a process wherein analyte is embedded in a solid or crystalline "matrix" of light-absorbing molecules (e. g., **nicotinic, sinapinic, or 3-hydroxypicolinic acid**) (col. 6,11. 15-25). Hydrophobic and hydrophilic MALDI ionization surfaces, such as metals (**gold, copper, stainless steel**), glass, silica, nylon and other synthetic polymers, agarose and other carbohydrate polymers, and plastics are disclosed as surfaces for actively capturing analyte (col. 6,11. 38-44). Other capture regions are disclosed, such as **surface of a bead, particle** or planar support treated with a bifunctional cross-linking reagent. "According to the practice of the present invention, a capture region may be formed in any microstructure surface in the sample preparation compartment by linking an analyte binding partner directly to the surface, and on MALDI ionization surfaces integrated with the preparation compartment. Alternatively, a capture region may be formed on the surfaces of beads, which can be chemically attached to the surface of the support, or magnetically attached by using magnetically responsive beads and applying a magnetic field to anchor the beads to the desired region of the support. Magnetically responsive beads and particles are well-known in the art and are commercially available from, for example, Dynal. RTM., Inc. (Lake Success, N.Y.) and Bangs Laboratories, Inc. (Carmel, Ind.)" (col. 7, 11. 30-43).

It would have been obvious at the time the invention was made to a person having ordinary skill in the art to use any of the materials described by Hancock in Nicola-Hayes' or Vestal-Vorm-Hayes' methods, because Hancock discloses them as suitable materials for performing MALDI-MS analysis of biological materials, specifically DNA.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Yelena G. Gakh
1/12/05